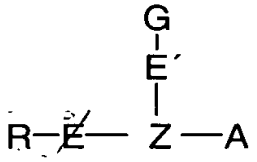
CLAIMS

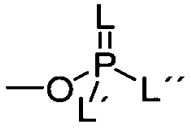
1. A labeling reactant of formula (I) suitable for labeling an oligonucleotide



(I)

characterized in that

R is a temporary protecting group such as 4,4´dimethoxytrityl (DMTr), 4-methoxytrityl (MMTr), trityl (Tr), (9-phenyl)xanthen-9-yl (pixyl) or not present;

A is either a phosphorylating moiety  where

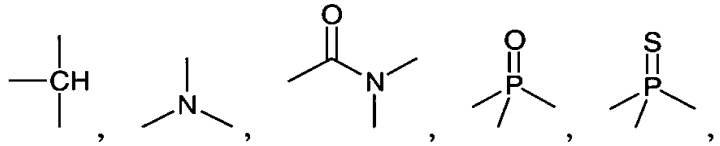
L is O, S, or not present

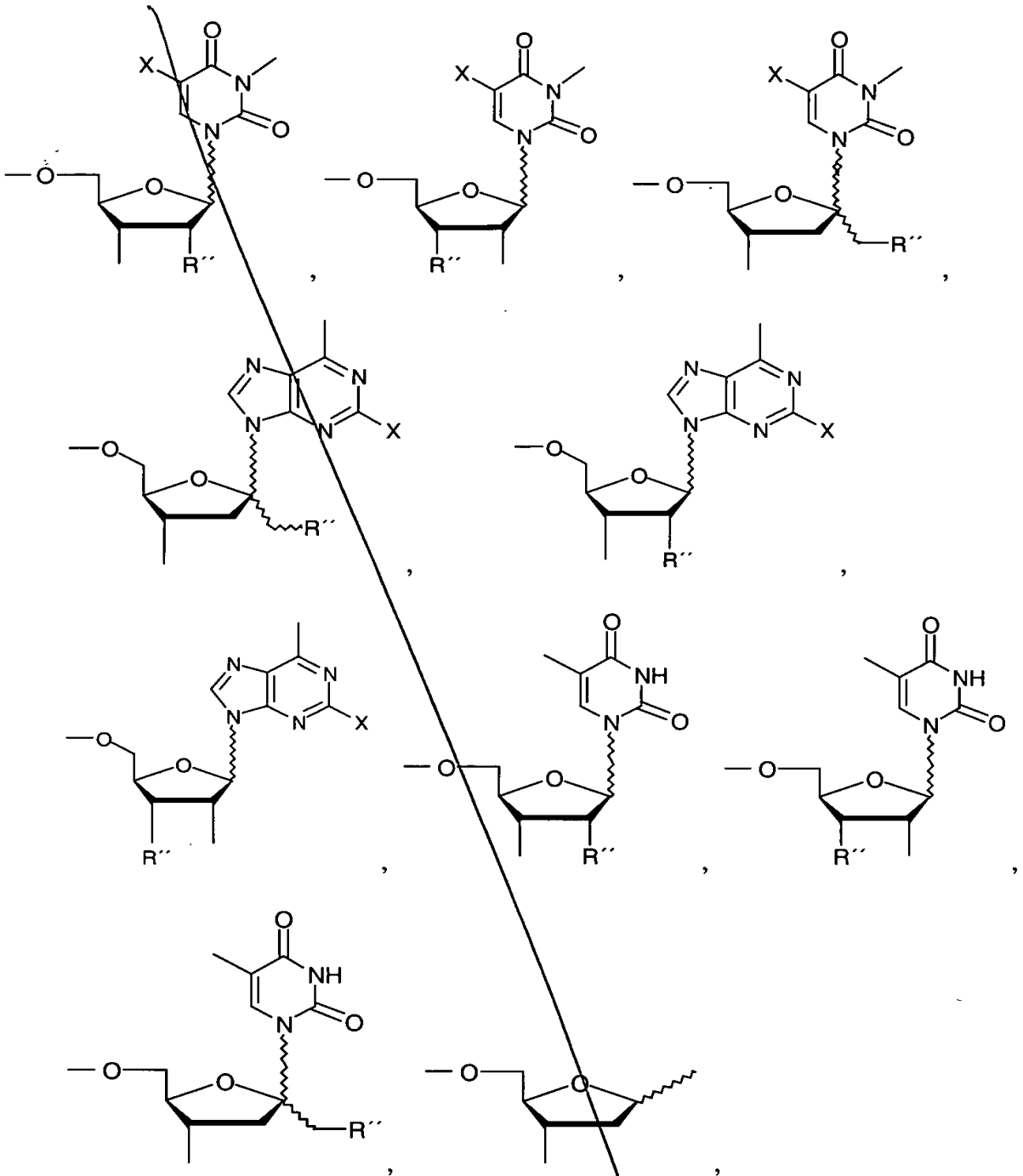
L´ is H, L´´´CH_2CH_2CN or L´´´Ar, where Ar is phenyl or its substituted derivative, where the substituent is nitro or chlorine, and L´´´ is O or S;

L´´ is O^-, S^-, Cl, $N(i\text{-}Pr)_2$; or

A is a solid support tethered to **Z** via a linker arm, which is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1–12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR´- and -NR´-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R´), wherein R´ represents an alkyl containing less than 5 carbon atoms;

Z is a bridge point and is formed from





or trivalent derivatives, substituted or unsubstituted, of cyclohexane, cyclohexene,cyclohexadiene, phenyl, cyclopentane, cyclopentene, cyclopentadiene, cyclobutane, cyclobutene, cyclobutadiene, aziridine, diaziridine, oxetane, thietaneazete, azetidine, 1,2-dihydro-1,2-diazete, 1,2-diazetidine, furan, tetrahydrofuran, thiophene, 2,5-dihydrothiophene, thiolane, selenophene, pyrrole,

pyrrolidine, phosphole, 1,3-dioxolane, 1,2-dithiole, 1,2-thiolane, 1,3-dithiole, 1,3-dithiolane, oxazole, 4,5-dihydrooxazole, isoxazole, 4,5-dihydoisozaole, 2,3-dihydroisoxazole, thiazole, isothiazole, imidazole, imidazolidine, pyrazole, 4,5-dihydropyrazole, pyrazolidine, triazole, pyran, pyran-2-one, 3,4-dihydro-2H-pyran, tetrahydropyran, 4H-pyran, pyran-4-one, pyridine, pyridone, piperidine, phosphabenzene, 1,4-dioxin, 1,4-dithiin, 1,4-oxathiin, oxazine, 1,3-oxazinone, morpholine, 1,3-dioxane, 1,3-dithiane, pyridazine, pyrimidine, pyrazine, piperazine, 1,2,4-triazine, 1,3,5-triazine, 1,3,5-triaza-cyclohexane-2,4,6-trione; where

R´´ is H or X´X´´, where

X´ is -O-, -S-, -N-, ON- or -NH- and X´´ is a permanent protection group such as *t*-butyldimethylsilyl-, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl-, 1-[2-chloro-4-methyl)phenyl]-4-metoxypiperidin-4-yl-, 4-methoxytetrahydropyran-4-yl-, pthaloyl-, acetyl, pivaloyl-, benzoyl-, 4-methylbenzoyl, benzyl-, trityl or

X´ is -O- and X´´ is alkyl or alkoxyalkylalkyl;

X is H, alkyl, alkynyl, allyl, Cl, Br, I, F, S, O, $NHCOCH(CH_3)_2$, $NHCOCH_3$, NHCOPh, SPh_3, $OCOCH_3$ or OCOPh;

E is a linker arm between **R** and **Z**, and is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1–12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR´- and -NR´-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R´), wherein R´ represents an alkyl containing less than 5 carbon atoms, or not present;

E´ is a linker arm between **G** and **Z**, and is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1–12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR´- and -NR´-CO-), carbonyl (-CO-), ester (-COO- and -OOC-),

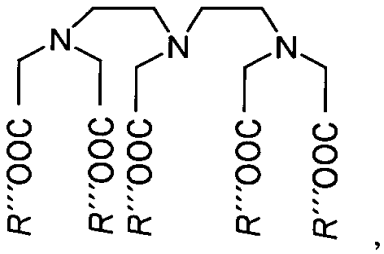
disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R´), wherein R´ represents an alkyl containing less than 5 carbon atoms, or not present;

G is a bivalent aromatic structure, tethered to two iminodiacetic acid ester groups $N(COOR'''')_2$, where

R´´´´ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and

said bivalent aromatic structure is capable of absorbing light or energy and transferring the excitation energy to a lanthanide ion after the solid phase synthesis made labeling reactant has been released from the used solid support, deprotected and converted to a lanthanide chelate, or

G is a structure selected from a group consisting of



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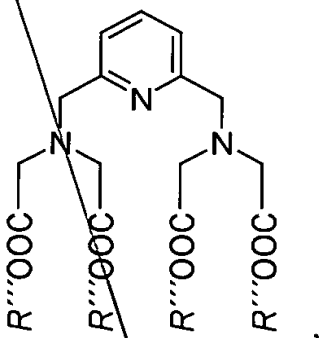

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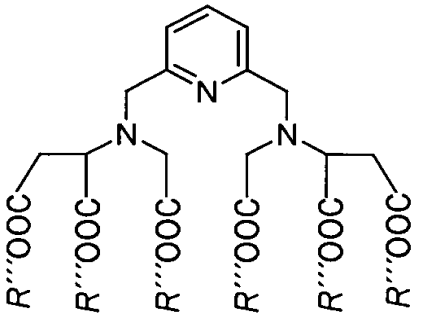

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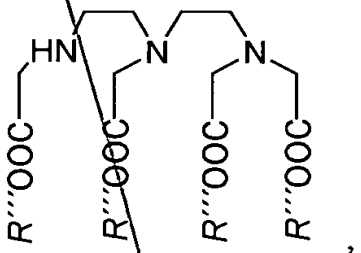

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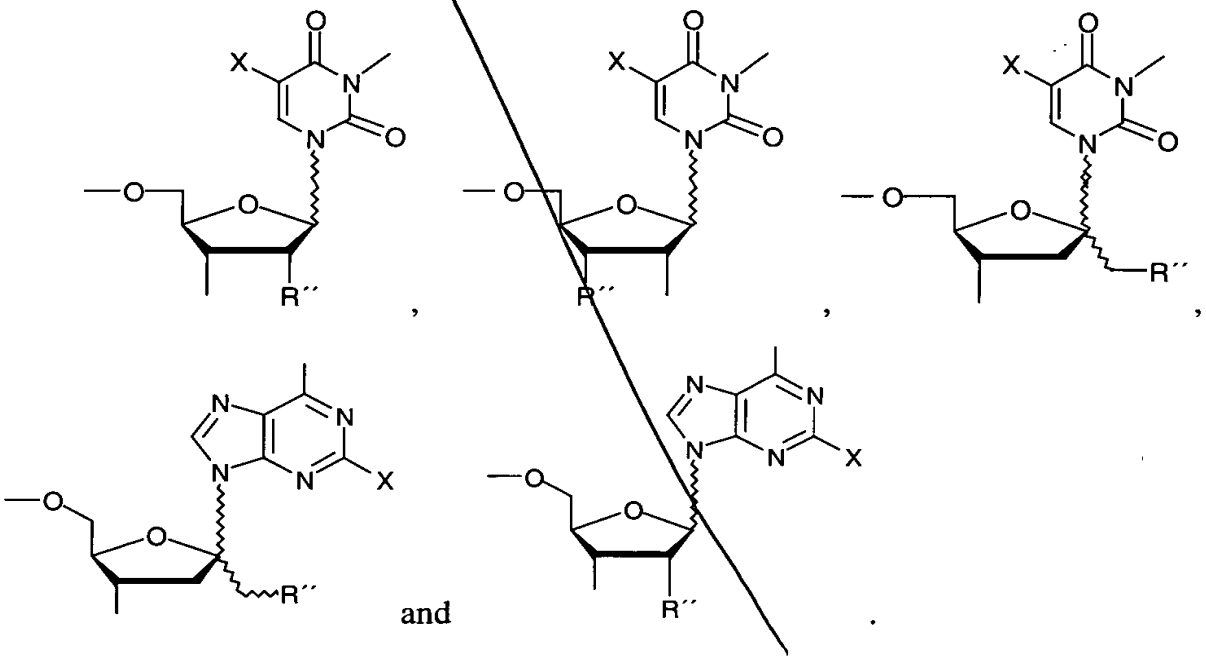
where

R´´´´ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and

one of the hydrogen atoms is substituted with E´, or

G is a protected functional group, where the functional group is amino, aminooxy, carboxyl, thiol, and the protecting group is pthaloyl, trityl, 2-(4-nitrophenylsulfonyl)ethoxycarbonyl, fluorenylmethyloxycarbonyl, benzyloxycarbonyl or *t*-butoxycarbonyl for amino and aminooxy, alkyl for carbonyl and alkyl or trityl for thiol provided that bridge point **Z** is selected from a group consisting of



and

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2. The labeling reactant according to claim 1 **characterized** in that **G** is a protected functional group and said group is preferably selected from the group consisting of amino, carboxyl, aminooxy and thiol.

3. The labeling reactant according to claim 1 suitable for monolabeling **characterized** in that **G** is an organic dye and preferably selected from the group consisting of dabsyl, dansyl, fluorescein, rhodamine and TAMRA.

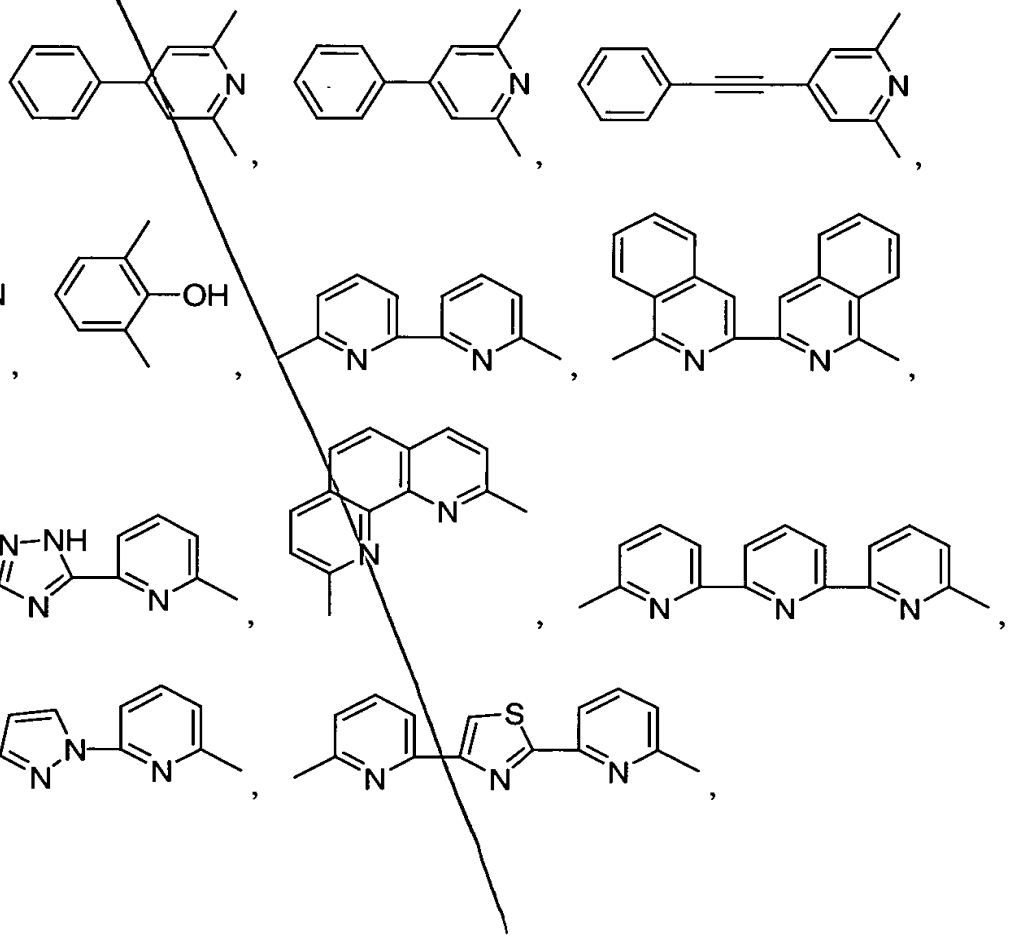
4. The labeling reactant according to claim 1 **characterized** in that the temporary protecting group **R** is 4,4'dimethoxytrityl.

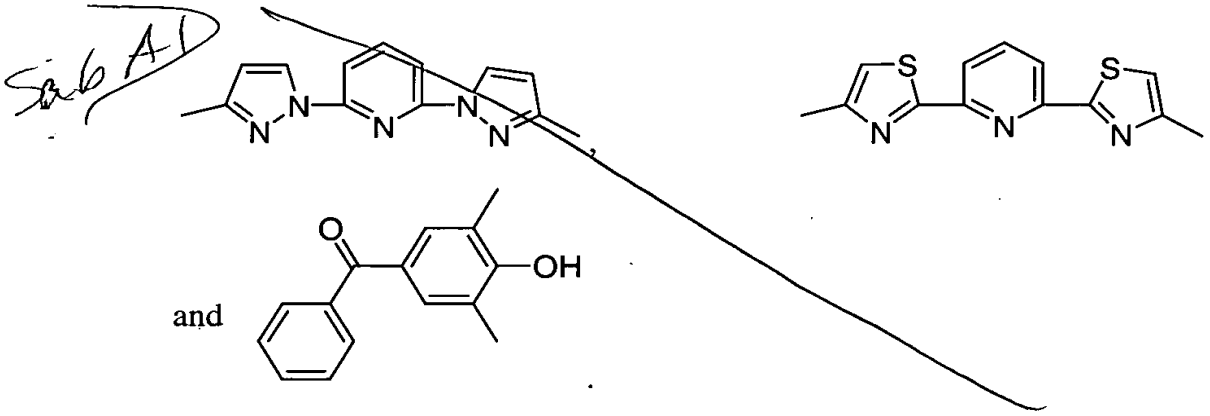
5. The labeling reactant according to claim 1 **characterized** in that said reactant is a nucleotide and the sugar of the nucleotide is preferably ribose or 2-deoxyribose.

6. The labeling reactant according to claim 5 **characterized** in that said sugar is a ribose and the permanent protecting group X´´ of X´, which is hydroxyl, is preferably selected from a group consisting of *t*-butyldimethylsilyl, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl- (Fpmp), 1-[2-chloro-4-methyl)phenyl]-4-methoxypiperidin-4-yl- or 4-methoxytetrahydropyran-4-yl-.

7. The labeling reactant according to claim 5 **characterized** in that said sugar is a ribose and X´´ is an alkyl or alkoxyalkyl, preferably methyl, methoxymethyl or etoxymethyl.

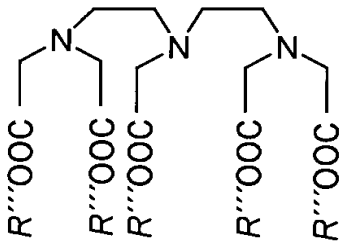
8. The labeling reactant according to claim 1 **characterized** in that G is a bivalent aromatic structure and preferably selected from a group consisting of

carbostyryl, 



and

9. The labeling reactant according to claim 1 **characterized** in that it is non-luminescent and G is selected from a group consisting of



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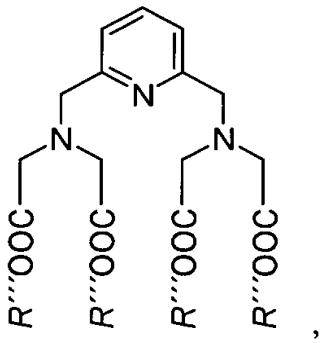

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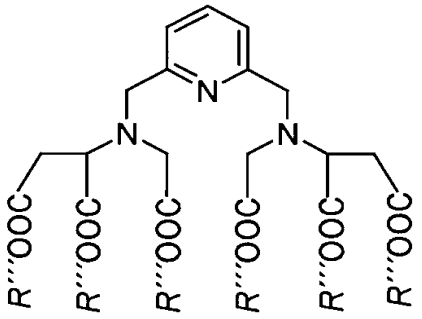

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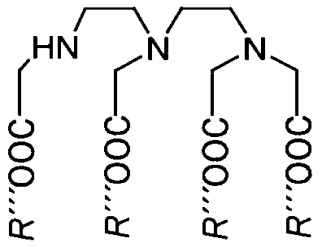

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where

R‴ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and one of the hydrogen atoms is substituted with E′.

10. The labeling reactant according to claim 9 **characterized** in that R‴ is selected from a group consisting of methyl, ethyl and allyl.

11. The labeling reactant according to claim 1 **characterized** in that the labeling reactant is selected from a group consisting of

2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-*N3* {tetramethyl 2,2′,2″,2‴-[(4-(1-hexyn-5-yl)pyridine-2,6-diyl)bis(methylennenitrilo)}tetrakis(acetato) uridine 3′-*O*-(2-cyanoethyl *N,N*-diisopropyl) phosphoramidite (**7**),

*N*3-[6-[4-(dimethylamino)azobenzene-4′-sulfonamido]hex-1-yl-5′-*O*-(4,4′-dimethoxytrityl)thymidine 3′-*O*-(2-cyanoethyl *N,N*-diisopropyl) phosphoramidite (**12**),

5′-*O*-(4,4′-dimethoxytrityl)-*N3*-{tetramethyl-2,2′,2″,2‴-{6,6′-[4′-hydroxyethoxyethoxyphenylethynyl]pyridine-2,6-diyl}bis(methylenenitrilo)tetrakis(acetato)}-thymidine 3′-*O*-(2-cyanoethyl *N,N*-diisopropyl) phosphoramidite (**18**),

tetramethyl-2,2′,2″,2‴-{{6,6′-[4-(6-hydroxyhexyl)-1*H*-pyrazol-1,3-diyl]bis-(pyridine)-2,2′-diyl}bis(methylenenitrilo)}tetrakis(acetato)-6-O-(2-cyanoethyl) *N,N*-diisopropyl)phosphoramidite (**25**)

2′-deoxy-5′-*O*-(4,4′-dimethoxytrityl)-3-6-{{4-{6,6″-bis[N,N-bis(methoxycarbonylmethyl)aminomethyl]-2,2′:6′,2″-terpyridine-4′-yl}phenyl}hex-5-yn-1-yl}-uridine 3′-[*O*-(2-cyanoethyl)-N,N-diisopropyl]phosphoramidite (**37**), and

tetramethyl 2,2′,2″,2‴-{[4′-(4″-(6-oxy-2-hexyn-1-yl)phenyl)-2,2′:6′,2″-terpyridine-6,6″-diyl]bis (methylenenitrilo)}tetrakis(acetato)-(2-cyanoethyl N,N-diisopropyl) phosphoramidite (**38**).

12. The labeling reactant according to claim 1 **characterized** in that **A** is a solid support preferrably 5′-*O*-(4,4′-dimethoxytrityl)-3′-O-succinyl-*N3*-{tetramethyl-2,2′,2″,2‴-{6,6′-[4′-hydroxyethoxyethoxyphenylethynyl]pyridine-2,6-diyl}bis-(methylenenitrilo)tetrakis(acetato)}thymidine long chain alkylamine controlled pore glass (**24**).

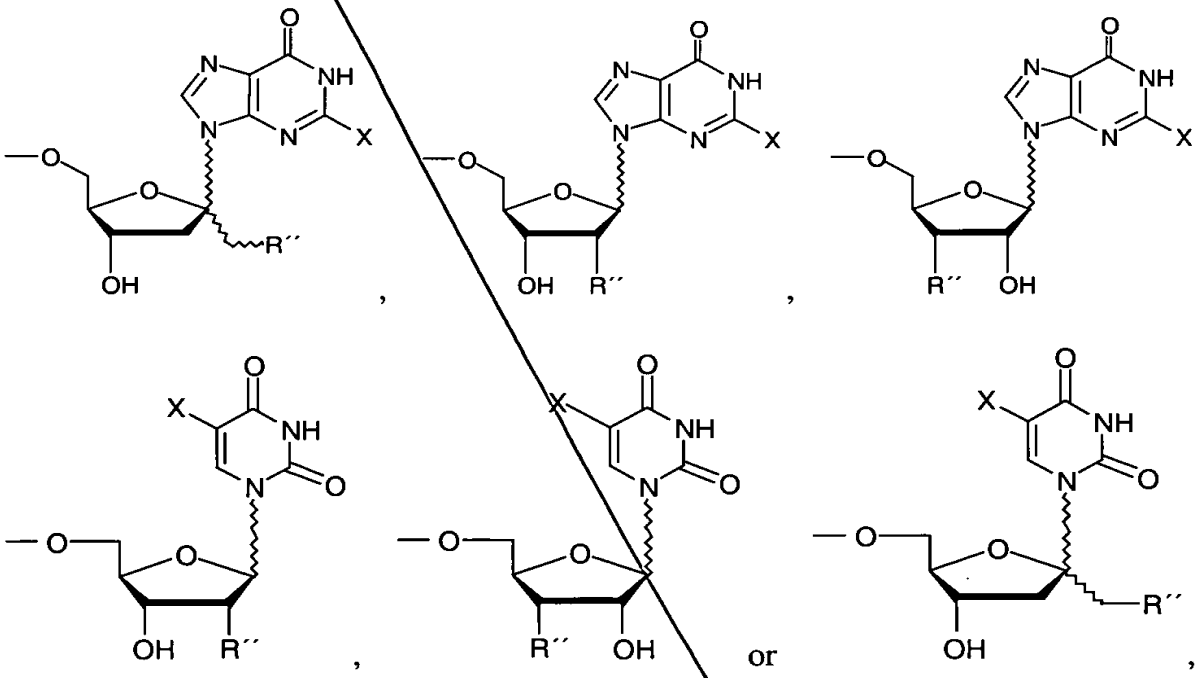
13. A method for direct attachment of a conjugate group to an oligonucleotide structure enabling the attachment of a desired number of these groups during chain assembly **characterized** in that it comprises a Mitsunobu alkylation of a compound of formula (II)

R— Z′ (II)

wherein

R is a temporary protecting group such as DMTr, MMTr, Tr or pixyl;

Z′ is an acidic bridge point selected from a group consisting of



where

R″ is H or X′X″, where X′ is -O-, -S-, -N-, ON- or -NH- and X″ is a permanent protection group such as *t*-butyldimethylsilyl-, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl-, 1-[2-chloro-4-methyl)phenyl]-4-metoxypiperidin-4-yl-, 4-methoxytetrahydropyran-4-yl-, pthaloyl-, acetyl, pivaloyl-, benzoyl-, 4-methylbenzoyl, benzyl-, trityl or alkyl;

X is H, alkyl, alkynyl, allyl, Cl, Br, I, F, S, O, $NHCOCH(CH_3)_2$, $NHCOCH_3$, NHCOPh, SPh_3, $OCOCH_3$ or OCOPh;

and pK_a of said acidic bridge point is <14;

with a compound of formula(III)

G—E´´ (III)

wherein

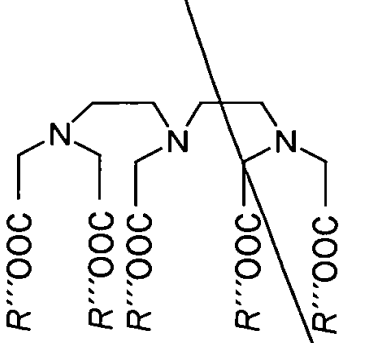
E´´ is an arm with a primary aliphatic OH group at the end, which arm is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1–12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR´- and -NR´-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R´), wherein R´ represents an alkyl containing less than 5 carbon atoms;

G is a bivalent aromatic structure, tethered to two iminodiacetic acid ester groups $N(COOR´´´)_2$, where

R´´´ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted and

said bivalent aromatic structure is capable of absorbing light or energy and transferring the excitation energy to a lanthanide ion after the solid phase synthesis made labeling reactant has been released from the used solid support, deprotected and converted to a lanthanide chelate, or

G is a structure selected from a group consisting of



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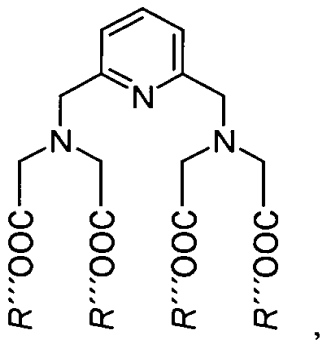

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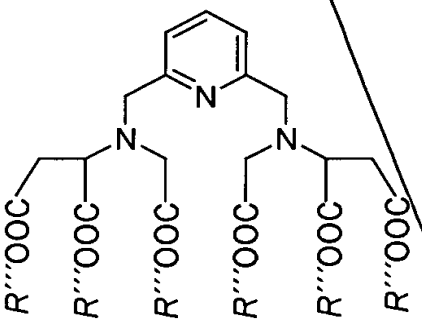

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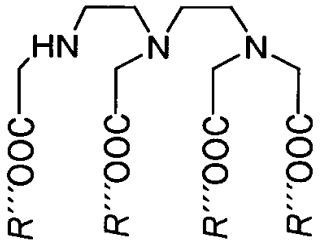

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where

R‴ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and

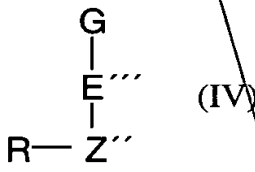
one of the hydrogen atoms is substituted with E′, or

G is a protected functional group, where the functional group is amino, aminooxy, carboxyl, thiol, and the protecting group is pthaloyl, trityl, 2-(4-nitrophenyl-sulfonyl)ethoxycarbonyl, fluorenylmethyloxycarbonyl, benzyloxycarbonyl or *t*-butoxycarbonyl for amino and aminooxy, alkyl for carbonyl and alkyl or trityl for thiol, or

G is not present; and

the functional groups of E′ and G, excluding said primary aliphatic OH group, are protected;

to produce compound of formula (IV)

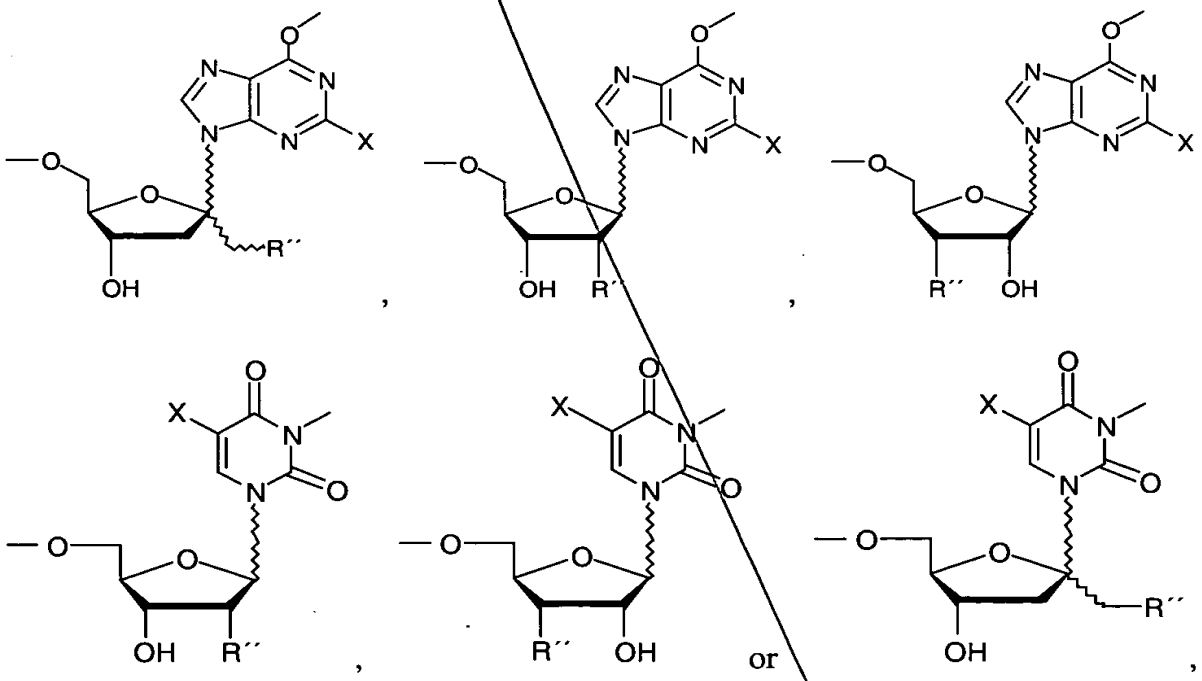


(IV)

wherein G and R of compound (IV) are as defined above;

E‴ is a linker arm between **G** and **Z**, and is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1–12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR´- and -NR´-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R´), wherein R´ represents an alkyl containing less than 5 carbon atoms; and

Z´´ is a bridge point selected from a group consisting of



or

where

R´´ is H or X´X´´, where X´ is -O-, -S-, -N-, ON- or -NH- and X´´ is a permanent protection group such as *t*-butyldimethylsilyl-, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl-, 1-[2-chloro-4-methyl)phenyl]-4-metoxypiperidin-4-yl-, 4-methoxytetrahydropyran-4-yl-, pthaloyl-, acetyl, pivaloyl-, benzoyl-, 4-methylbenzoyl, benzyl-, trityl or alkyl;

X is H, alkyl, alkynyl, allyl, Cl, Br, I, F, S, O, $NHCOCH(CH_3)_2$, $NHCOCH_3$, NHCOPh, SPh_3, $OCOCH_3$ or OCOPh.